REMARKS

Claims 33-39 and 42-50 are currently pending in the present application. Claims 33, 34 and 37-39 have been currently amended, and new claims 42-50 have been added to more particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

It is respectfully submitted that the amendments made and the new claims added herein are supported by the Specification and the original claims. For example, support for the new claims 42-45 can be found in the originally filed claim 3 and the originally filed Specification, paragraph [0022]. Accordingly, the amendments made herein introduce no new subject matter. Additionally, no additional claims fees are necessitated. A complete listing of all claims ever presented in accordance with 37 C.F.R. §1.121(c)(1) is set forth herein. Entry of the amendments made herein is proper and respectfully requested in view of the accompanying RCE Request, which withdraws the finality of the Office Action. Reconsideration of the captioned application based on the amendments and following remarks is respectfully requested.

In the Office Action, the Examiner has maintained the rejection of claim 37 under 35 U.S.C. §112, first paragraph, for the lack of enablement for inhibiting all tumor activities. The Examiner has also objected to claims 33-39 as containing non-elected subject matter.

Applicant appreciates the Examiner's courtesy in conducting multiple telephone interviews with Applicant's representatives regarding the present application. During the telephone interview on November 16, 2006, the rejection of claim 37 was first discussed. Applicant's representatives argued that claim 37 is enabled in view that antitumor and antimetastatic activities had been shown for various Ruthenium complexes in the prior art, and that the Specification and the Applicant's Declaration filed on June 5, 2006 (hereinafter "Declaration") had demonstrated that Ruthenium complexes of the present application indeed have anti-tumor activity against a list of representative tumors. The Examiner maintained that a method directed at treating all tumors with a composition of the present invention was too broad and the inclusion of a list of tumors was required to obviate the rejection. He agreed that the list may include tumors listed in Table 1 and Table 2 of the Declaration and some publications. The objections to claims 33-39 were also discussed during the telephone interview. The Applicant's

representatives argued that B and B' should not be limited to "imidazol, pyazole, triazol, or indazol" because B and B' had already been specifically defined as "basic heterocycles with one or more nitrogen atom" in the claims. The Examiner maintained the objections.

During the telephone interview on January 12, 2007, a list of amended claims were discussed. The Examiner indicated that claims 33-36, 38-39 and 42-45 presented on the list, which were identical to the respective claims set forth herein, appeared to be acceptable. He suggested additional modifications to claim 37 recited on the list, including, for example, by replacing "inhibiting tumor activity" with "treating a tumor", in the preamble. Support for this change can be found, for example, in paragraphs [0010] and [0081] of the originally filed Specification. This change and other modifications suggested by the Examiner have been incorporated in the currently pending claim 37.

As described throughout the originally filed Specification, embodiments of the invention provide a reaction product mixture, *i.e.*, compounds of formula (III) and compounds of formula (IV), along with, for example, excess reactant(s), which enhances the solubility of various salts of Ruthenium (Ru) complexes for the intended use of treating various tumors. The knowledge present in the prior art was that antitumor and antimetastatic activity had been shown for different Ru complexes, see for example, Peti et al., *Eur J. Inorg. Chem.* 1999, 1551-1555, WO9736595, US4843069, and references therein, and that one can follow standard procedures to test the anti-tumor activity of a compound both *in vivo* and *in vitro*, see Declaration. The originally filed application conveyed to one skilled in the art that the Ru complexes of the present invention have anti-tumor activity, as illustrated by results of *in vitro* cell growth assay on two different types of tumor cells, SW480 (colon carcinoma) and CH1 (ovarian carcinoma). The Declaration presented additional data showing that compounds of the invention have antitumor activity on many different types of tumors when tested both *in vivo* and *in vitro* following standard procedures. Accordingly, Applicant submits that sufficient detail has been provided to show one of ordinary skill in the relevant art that Applicant invented a method of treating any type of tumors with a composition of the present invention, and that one of ordinary skill in the art, upon reading the Specification, would be capable of and enabled to design and carry out any protocol or clinical design experiment as may be necessary and expected for

determining an appropriate dosage, regimen and/or route of administration for treating any type of tumors.

Solely to advance the examination of the application, claim 37 has been amended, upon Examiner's suggestion, to include a list of tumors. The amendment does not represent an acquiescence in any ground of the rejection. Applicant reserves the right of filing of one or more divisional applications directed to the cancers/tumors not listed in the amended claim 37.

Enablement for the treatment of a tumor listed in claim 37 with a claimed composition can be found from the Specification, Table 1 and Table 2 of the Declaration (hereinafter referred to as "Table 1" and "Table 2", respectively) and publications. Although some of the listed tumors are enabled by multiple sources, for clarity, below only one representative source for each tumor listed in the amended claim 37 is discussed in relevant parts.

The originally filed application conveyed to one skilled in the art that the Ru complexes of the present invention have anti-tumor activity, as illustrated by results of *in vitro* cell growth assay on two different types of tumor cells, SW480 (**colon carcinoma**) and CH1 (**ovarian carcinoma**).

Table 1 summarizes the dosages and results of a Clinical Phase I study from eight patients in an open dose-escalation-study with "Combination I", a mixture of sodium-*trans*-[tetrachlorobis (1*H*-indazole) ruthenate (III)] and indazole-hydrochloride. The eight patients had different types of tumors including, **colorectal tumors** (i.e., sigmoid colon adenocarcinoma, rectum adenocarcinoma, and colon adenocarcinoma), a **bladder carcinoma**, a **liver cancer**, an **endometrioma**, a spindle bcell **melanoma**, and a **tongue carcinoma**. The results showed that responses to the treatment were observed over a comparable broad range of dosages in a variety of tumors. The results also demonstrated that one of ordinary skill in the art can readily design an *in vivo* protocol necessary for determining the dosage level appropriate for stabilizing and/or inhibiting further growth of any type of tumors.

Table 2 summarizes the results of *in vitro* cell growth inhibition studies on various tumor cell lines treated with Combination I. The cell lines tested include a cell line of an **epidermoid carcinoma, prostate carcinoma, colon carcinoma, lung carcinoma, renal cell carcinoma**, and **melanoma**. The results showed that one of ordinary skill in the art can readily design an *in vitro* protocol to assist in determination of an appropriate dosage and regimen for inhibiting the growth of any tumor cells.

In addition, various publications describe the anti-tumor activities of Ru complexes, see for example, Heffeter et al. *J Pharmacol Exp Ther.* 2005 Jan;312(1):281-9. Epub 2004 Aug 26 (hereafter "Heffeter et al."), describing that KP1019, a Ru complex based on which a composition (KP1339) of the present invention was developed (see Example 1 of the Specification), induces cytotoxicity in various tumor cells, including the **leukemia** cell line HL60 and the **breast adenocarcinoma** cell lines MCF-7 and MDA-MB-231; Djinovic et al. *J Inorg Biochem.* 2004 Dec;98(12):2168-73 (hereafter "Djinovic et al."), describing that a ruthenium (III) complex $K2[Ru(dmgly)C_{l4}].2H_2O$ is toxic to C6 **astrocytoma** cell line, but not to primary rat astrocytes; Van Rensburg et al. *Anticancer Res.* 2002 Mar-Apr;22(2A):889-92 (hereafter "Van Rensburg et al."), describing cytotoxicity of a series of water-soluble mixed valent diruthenium tetracarboxylates against HeLa (a **cervical carcinoma** cell line) and multidrug resistant CoLo 320DM human cancer cell lines; and Gaiddon et al. *J Pharmacol Exp Ther.* 2005 Dec;315(3):1403-11. Epub 2005 Sep 16 (hereafter "Gaiddon et al"), describing that ruthenium (II)-derived compounds led to G1 arrest and induced apoptosis in tumor cell lines derived from **glioblastomas** (HS683), **neuroblastomas** (N2A, SH5Y), **lymphoid tumors** (RDM4, TK6), and **adenocarcinoma** (HCT116).

The following Table recites a representative source for each tumor listed in claim 37.

Tumor Listed in Claim 37	Source
a breast cancer	Heffeter et al (2005)
an ovarian cancer	Specification CH1

a lung cancer	Table 2
a colorectal tumor	Table1/2 and Specification
a prostate cancer	Table 2
a melanoma	Table 2
a liver cancer	Table 1
an astrocytoma	Djinovic et al. (2004)
a neuroblastoma	Gaiddon et al. (2005)
a leukemia	Heffeter et al. (2005)
an epidermoid carcinoma	Table 2
a cervical carcinoma	Van Rensburg et al. (2002)
a bladder carcinoma	Table 1
an endometrioma	Table 1
a tongue carcinoma	Table 1
a glioblastoma	Gaiddon et al. (2005)
a lymphoid tumor	Gaiddon et al. (2005)
a renal cell carcinoma.	Table 2

In view of the above discussion, Applicant submits that the amended claim 37 has written description support and is fully enabled. One skilled in the relevant art would have reasonably believed that the Applicant, at the time the application was filed, had possession of the claimed invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are respectfully requested.

To overcome the objections to claims 33-39, the claims have been amended, upon Examiner's suggestion, to cancel the non-elected subject matter, without prejudice to the filing

of one or more divisional applications directed to the canceled subject matter thereof. Accordingly, reconsideration and removal of the objection are respectfully requested.

In view of the Remarks set forth herein and the amendments to the claims, Applicant respectfully submits that the pending claims are enabled, comply with the written description requirement, are definite and patentably distinguish over the prior art of record and known to Applicant. Accordingly, reconsideration, withdrawal of all rejections and objections and a Notice of Allowance are respectfully requested.

Respectfully submitted,
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WWS/WH
Enclosures – Petition for Extension of Time (two months) and a RCE under 37 C.F.R. § 1.114.